

Versatile controlled ion release for synthesis of recoverable hybrid hydrogels with high stretchability and notch-insensitivity†

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A versatile ion release mediated by GDL is demonstrated to achieve a controlled homogeneous crosslinking of alginate chains, which is critical for the synthesis of highly stretchable and notch-insensitive hybrid hydrogels with controlled properties.

Hydrogels with outstanding strength and toughness have been attracting great research interest for both scientific and practical purposes.^{1,2} Non-covalent interactions, such as polyampholyte complexation,¹ ion/polymer chelation,³ hydrophobic associations,⁴ and polymer/clay adsorption⁵, have been widely utilized as reversible sacrificial bonds, which could dissipate energy upon loading and recover afterwards under suitably controlled conditions.^{1,3} Besides, the distribution of such sacrificial crosslinking units has been recognized to be critical for energy dissipation in the network. For example, mobile figure-of-eight crosslinks with re-adjustable distribution provide slide-ring hydrogels with very high stretchability.⁶ It remains a challenge to synthesize tough and stretchable hydrogels with well controlled sacrificial units.

Hydrogels based on ion-chelated polysaccharides,^{3,7} synthetic polymers⁸ or nanoparticles⁹ have shown outstanding stretchability and capability to recover or heal. For example, hybrid hydrogels, comprised of ionically crosslinked alginate chains and interpenetrated elastic networks,^{2,3} have been widely reported with excellent mechanical properties as well as biocompatibility. Linear alginate chains are comprised of consecutive (1,4)-linked β -D-mannuronate (M) blocks or α -L-guluronate (G) blocks, or alternating M and G blocks.³ The adjacent G blocks are able to quickly chelate divalent or multivalent ions, resulting in ion-crosslinked hydrogels.¹⁰ Such a quick chelation and high

viscosity of alginate solutions usually make it difficult to control the network structures and mechanical properties.¹¹ In order to resolve these problems, it is desirable to control the ion distribution in the solutions and the gelation kinetics.

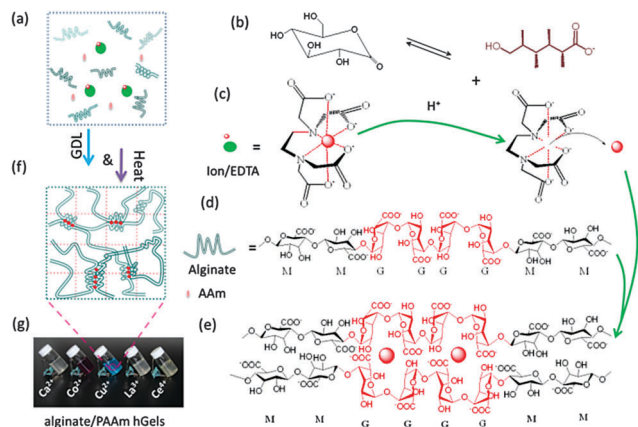
The controlled release of ions has been used to synthesize alginate hydrogels. For example, the hydrolysis of glucono delta-lactone (GDL) is known to generate H^+ , which has been used to trigger slow release of Ca^{2+} from insoluble salts ($CaCO_3$).¹² Such a controlled Ca^{2+} release allows for the use of very high concentration alginate solutions to gain high strength and toughness.¹² However, the insoluble $CaCO_3$ particulates are not well distributed in the alginate solutions. In another study, a UV triggered Ca^{2+} release from photosensitive nitr-T cages has been used to prepare hydrogels with alginate concentration up to 10 wt%, allowing for convenient tuning of the mechanical properties.¹¹ Such ion release and ionic crosslinking of alginate are insensitive to other chemicals.^{11,12} These studies illuminated a strategy to synthesize hybrid hydrogels with well-controlled network structures and mechanical properties.

In this communication, we demonstrate a versatile *in situ* control of multivalent ion (*i.e.*, Co^{2+} , Cu^{2+} , Ca^{2+} , La^{3+} and Ce^{4+}) release to crosslink alginate chains by using GDL to trigger decomposition of ion/EDTA coordinates. Herein, the ion/EDTA coordinates serve as soluble ion reservoir and form a homogeneous mixture with viscous sodium alginate solutions. The EDTA coordinates are stable with alginate due to the high ion-EDTA chelating constant (for example, Ca^{2+} /EDTA has a chelating constant of 4.47×10^{10} with Ca^{2+} , much higher than that of Ca^{2+} /G blocks¹¹). No gelation occurred over months. On the other hand, the ion/EDTA coordinates are known to decompose upon an exposure to H^+ .¹³ Therefore, a proton generator, GDL, is used as it releases H^+ upon its hydrolysis into gluconic acid in water (Scheme 1b).¹⁴ Thus, the ion release is triggered and the alginate chains are *in situ* crosslinked by the released ions (Scheme 1d and e). It is noted that GDL exhibits a high dissociation rate but a low hydrolysis rate,¹⁴ resulting in a slow pH decrease of the precursor sol. Therefore, it is convenient to

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Scheme 1 Schematic illustration to the synthesis of alginate/PAAm hybrid hydrogels (hGel). In the reactant mixture (a), GDL is hydrolyzed into gluconate ion and proton (b), which triggers the release of ions from EDTA cages (c). The released ions are *in situ* chelated by G blocks (d), leading to the formation of “egg-in” crosslinks (e and f). The alginate skeleton is further used to host polymerization of acrylamide monomers to generate hGels (g).

control the ion release rate and the gelation kinetics by varying the GDL concentration (C_{GDL}). Finally, the alginate hydrogels are used to host *in situ* free radical polymerization of a second monomer, yielding hybrid hydrogels with very high stretchability, toughness, and recoverability.

The hybrid hydrogel synthesis is a simple one-pot and two-step procedure. All the reactants, *i.e.*, 4 wt/vol% sodium alginate, 28 wt/vol% acrylamide (AAM) monomer, 50 mM ion/EDTA agents, 0.01 mol% potassium persulfate (KPS) and N,N' -methylenebisacrylamide (MBAA) with respect to AAM concentration were mixed into a homogeneous aqueous solution. No gelation was observed before the addition of GDL, according to rheological investigation by using a Physical MCR-301 instrument (Anton Paar, Austria) at a constant strain amplitude ($\gamma = 1\%$) and a fixed angular frequency (10 rad s^{-1}) at room temperature. Both storage modulus (G') and loss modulus (G'') of this solution remained almost constant over time, with G'' higher than G' , which is typical for a fluid (Fig. 1a). As 16.9 mM GDL solution was added into the reactant mixture, the G'' and G' values were gradually increased over time, with G'

increasing faster than G'' , resulting in a crossover at about 270 min (Fig. 1a). This crossover suggests the establishment of a crosslinked network, or a sol-gel transition. The crossover time is defined as the sol-gel transition time ($t_{\text{s-g}}$). As the C_{GDL} was increased from 16.9 to 33.7, 67.4, 85, and 100 mM, the $t_{\text{s-g}}$ value (of Alg-1 to Alg-5 gels) was decreased from 270.0 ± 6.2 to 223.4 ± 4.2 , 109.9 ± 1.3 , 23.9 ± 0.9 , and 15.2 ± 1.7 min (Fig. 1b). Meanwhile, the modulus of the gels became higher. Interestingly, such a controlled release strategy even allows for the use of saturated sodium alginate solution to prepare hydrogels. These results suggest a convenient control of the gelation kinetics and mechanical properties of hydrogels, which has been long pursued for the synthesis of hydrogels with high strength and toughness.

Subsequently, the Ca^{2+} /alginate network was used to host free radical polymerization of AAM monomers in a water bath at 70°C to generate alginate/PAAm hybrid hydrogels (hGel). In order to investigate the critical role played by GDL-controlled ion release on the mechanical properties of hybrid hydrogels, the C_{GDL} was varied from 16.9 to 33.7, 67.4, 85, and 100 mM, while other reactants were kept constant. Correspondingly, the obtained hybrid hydrogels were designated as hGel-1, hGel-2, hGel-3, hGel-4, and hGel-5, respectively. As an example, the hGel-1 specimens (length: 30 mm, gauge width: 20 mm, gauge length: 10 mm, and thickness: 2.5 mm) were artificially notched (notch length 8 mm) in centre (Fig. 2a) or at the edge (Fig. 2b), and uniaxially stretched at a crosshead speed of 100 mm min^{-1} till fracture. At the initial stage, the notches remained stable and the tip became dramatically blunted without crack propagation. The notches then became widened and merged into the edges of the samples during further elongation. Similar notched tensile tests were conducted with artificial edge notches of 0.5, 8, 12 and 15 mm long (Fig. 2c). It is interesting that, even for a notch ratio as high as 75% (with respect to the sample width), the fracture elongation was as high as 250 mm (Fig. 2c). With a higher C_{GDL} , the fracture elongation was slightly decreased, while the fracture strength was highly increased. As a result, the rupture work was increased. As the sample was stretched to 500% (below the fracture strain), the centre-notched hydrogels could recover to its initial shape for more than ten successive loading-unloading cycles, while negligible hysteresis was recognized in the following loading-unloading cycles (Fig. S1, ESI†). In contrast, the notched

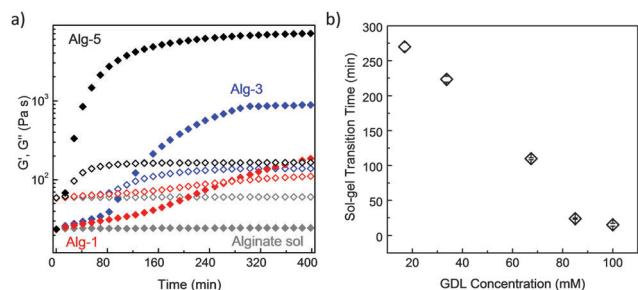


Fig. 1 (a) Rheological analysis of Ca^{2+} /EDTA and sodium alginate (Alg) mixture solution with different GDL concentrations: 16.9 mM for Alg-1, 67.4 mM for Alg-3 and 100 mM for Alg-5. (b) The dependence of sol-gel transition time on the GDL concentration.

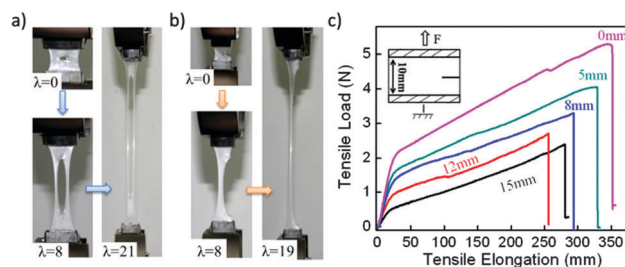


Fig. 2 Photographs of Ca^{2+} /alginate gel (hGel-1) stretched with 8 mm artificial notches in centre (a) and at edge (b). (c) Typical tensile load-elongation curves of edge notched (inset) hGel-1 stretched with notch length of 0, 5, 8, 12 and 15 mm.

PAAm hydrogel was ruptured within 400% strain in spite of the notch length (Fig. S2, ESI[†]). The notch blunting, probably due to the unzipping of Ca^{2+} /alginate coordinates,³ suggests a capability to dissipate energy at crack tips, which is essentially critical for the high strength and toughness.

The effect of GDL-controlled ion release on the tensile properties of hGels was systematically investigated. Standard dumbbell-shaped samples (gauge width: 2 mm, gauge length: 20 mm, thickness: 2–2.5 mm) were uniaxially stretched at a crosshead speed of 100 mm min⁻¹. Fig. 3a shows the representative stress–strain curves. The slope of the curves between 10–50% strain was used to calculate the tensile modulus. The fracture energy or toughness was defined as the area under the ultimate stress–strain curve.¹⁵ All hybrid hydrogels yielded at 110–120% strain. As the C_{GDL} was increased from 16.9 to 67.4 mM, the modulus was monotonically increased from 34.8 ± 1.0 to 52.6 ± 1.7 kPa, while the fracture strength (σ_f) was increased from 276.3 ± 29.9 to 459.9 ± 43.4 kPa. Meanwhile, the fracture elongation (ε_f) was decreased from $2560 \pm 60\%$ to $2160 \pm 70\%$ (Fig. 3b). As a result, the tensile toughness was increased from 3.1 to 5.1 MJ m⁻³. These results suggest that a higher C_{GDL} causes more ion release, which sequentially results in higher energy dissipation to unzip the Ca^{2+} /alginate network.

Once the network was unzipped, no immediate recovery was possible. For example, as the hGel-1 sample was stretched to 700% strain and unloaded, an immediate second loading–unloading test resulted in a negligible hysteresis loop. In order to re-establish (recover) the unzipped network, the tested hydrogels were heated at elevated temperatures (e.g., 80 °C) for different durations before cooling down to room temperature. Afterward, the restored samples were subjected to cyclic tests to 700% strain. Fig. 3c compares the cyclic loading–unloading loops of those hGel-5 samples restored at 80 °C for 0.5, 1, 2, 4, and 8 h. The loop area was gradually increased over time. The recovery extent, defined as the ratio of loop area after

heating to that for the first cycle, was summarized in Fig. 3d as a function of C_{GDL} and heating time. The recovery ratio was increased over time. On the other hand, with a higher C_{GDL} , the recovery ratio was higher (Fig. 3d and Fig. S3, ESI[†]), although the Ca^{2+} /EDTA concentration was constant in these hydrogels.

Finally, we emphasize that this GDL-mediated ion release method is versatile for many other multivalent ions to crosslink alginate chains and synthesize hybrid hydrogels. We used 50 mM metal ion/EDTA coordinates (where the ions are Co^{2+} , Cu^{2+} , La^{3+} , or Ce^{4+}), and 100 mM GDL for the synthesis of hybrid hydrogels following the formulations and procedures for the above-described Ca^{2+} /alginate hGels. The obtained hGels appeared purple, blue, white and light yellow due to the presence of Co^{2+} , Cu^{2+} , La^{3+} and Ce^{4+} ions (Fig. 4). These hydrogels, similar to those crosslinked by Ca^{2+} , showed outstanding notch blunting behaviour (Movies S1 and S2, ESI[†]), no matter they were notched in centre (Fig. 4a) or at edge (Fig. 4b). No fracture occurred with an extension ratio (λ) as high as 20 (Fig. 4b).

The influence of ion type on the uniaxial tensile properties of the hybrid hydrogels was investigated. Fig. 4c shows the tensile stress–strain curves of dumbbell-shaped hGels as prepared above, with ε_f higher than 2000% (Fig. 4d). The hybrid hydrogel based on Ca^{2+} /alginate chelation showed the highest modulus and lowest ε_f . Other than this, as the ion valency was increased from two to three and four, the tensile modulus was increased from 14.2 ± 1.6 kPa (Co^{2+}) to 16.1 ± 1.3 kPa (Cu^{2+}), 23.9 ± 0.7 kPa (La^{3+}) and 28.9 ± 0.9 kPa (Ce^{4+}). The σ_f was increased from 205.3 ± 3.2 kPa (Co^{2+}) to 255.2 ± 8.5 kPa (Cu^{2+}), 350.8 ± 8.5 kPa (La^{3+}), and 455.0 ± 49.4 kPa (Ce^{4+}). Correspondingly, the fracture strain was decreased from $2960 \pm 30\%$ (Co^{2+}) to $2950 \pm 30\%$ (Cu^{2+}), $2850 \pm 20\%$ (La^{3+}), and $2690 \pm 40\%$ (Ce^{4+}).

The influence of ion type on the mechanical properties of hybrid hydrogels is related to the capacity of ions to chelate

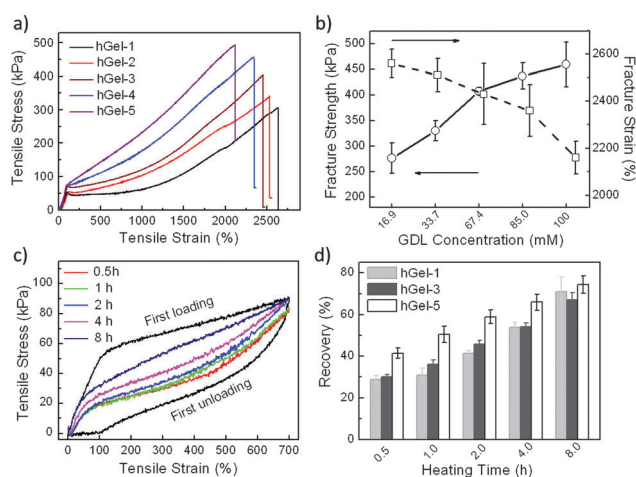


Fig. 3 (a) Typical tensile stress–strain curve of hybrid hydrogels (hGels). (b) The effect of GDL concentration on the tensile properties of hGels. (c) Representative tensile loading–unloading loops of hGel-1 upon first and subsequent tests after storage at 80 °C. (d) Recovery ratios of hGel-1, hGel-3 and hGel-5 at 80 °C for different times.

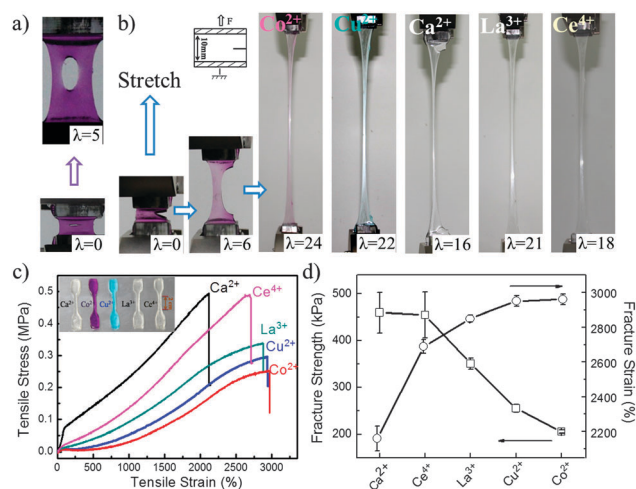


Fig. 4 Photographs of multiple ion crosslinked hGels stretched with 8 mm long artificial notches in centre (a) and at edge (b). (c) Typical tensile stress–strain curve of the alginate/PAAm hGels with multivalent ions (i.e., Co^{2+} , Cu^{2+} , Ca^{2+} , La^{3+} and Ce^{4+}). (d) The effect of diverse cations on the tensile properties of hybrid hydrogels.

with the alginate G blocks. In order to test this hypothesis, the swelling behaviour of these hybrid hydrogels was investigated. The Ca^{2+} -crosslinked hybrid hydrogel showed the lowest swelling, suggesting a highest crosslink density. Other than this, the swelling ratio was decreased with increasing ion valency (Fig. S4, ESI†). The crosslink density was higher for hydrogels with a lower swelling ratio. It is known that the coordination numbers (CNs) are 4 for Co^{2+} and Cu^{2+} , 6 for Ca^{2+} , and higher for La^{3+} and Ce^{4+} . With a higher CN, the crosslink density for La^{3+} and Ce^{4+} -crosslinked hybrid hydrogels was higher than those for Co^{2+} - and Cu^{2+} -crosslinked hybrid hydrogels. On the other hand, the charge density for Ce^{4+} is higher than La^{3+} , leading to a stronger chelation with G blocks and thus a higher crosslink density. Therefore, the modulus and σ_f are increased, and ε_f was decreased in the ion order of Co^{2+} , Cu^{2+} , La^{3+} , Ce^{4+} , and Ca^{2+} .

In conclusion, this work demonstrates the utilization of controlled ion release from ion/EDTA cages for the synthesis of alginate/PAAm hybrid hydrogels with very high stretchability, toughness, and recovery. It is critical that the ion/EDTA cages were homogeneously distributed in the hydrogel precursor solution. Such ion/EDTA was decomposed upon exposure to protons generated by the hydrolysis of GDL. The released ions formed *in situ* crosslinks with the alginate chains, leading to a homogeneous and rigid network, with the gelation kinetics and mechanical properties controllable by C_{GDL} . Such alginate hydrogel was used to host *in situ* free radical polymerization of monomers (*e.g.*, acrylamide), resulting in hybrid hydrogels with very high stretchability, toughness insensitivity to notches, presumably due to the unzipping of the ion/alginate chelation. The internal damage of tested hydrogels could be recovered, presumably due to the re-formation of ion/alginate chelation. This strategy has been demonstrated to be versatile for hydrogel

synthesis based on many other multivalent ions including Co^{2+} , Cu^{2+} , La^{3+} and Ce^{4+} . The crosslink density, swelling, and mechanical properties are strongly dependent on the chelation number and charge density of the ions. This novel controlled release strategy offers a convenient control of hydrogel synthesis, which is critical for such hybrid hydrogels to be used as injectable and/or 3D printing materials.²

This work was supported by Natural Science Foundation of China (21004074, 21574145), the Hundred Talents Program of the Chinese Academy of Sciences (J. F.), the Zhejiang Natural Science Foundation of China (LR13B040001, LY14B040001), and the Ningbo Natural Science Foundation (2014A610194).

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